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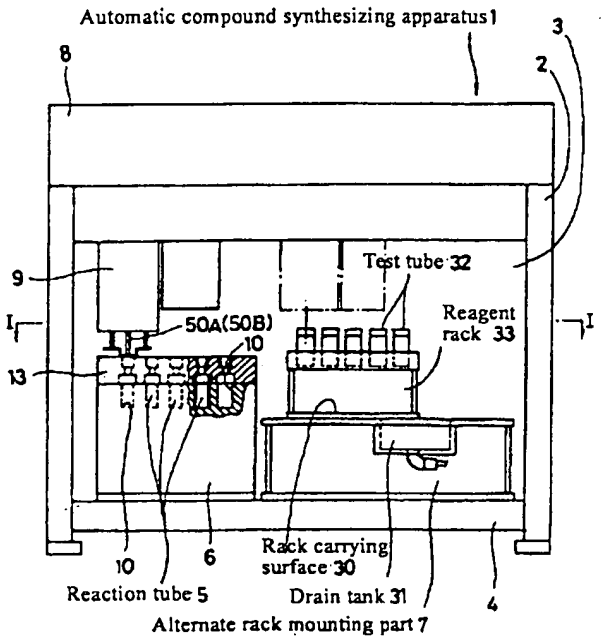
(54) **[Title of the Invention]**

AUTOMATIC COMPOUND SYNTHESIZING APPARATUS AND REACTION TUBE SEALING STRUCTURE USED IN THE SAME

(57) **[Abstract]**

[Object] The object of the present invention is to allow the automatic performance of various operations that are required in order to synthesize compounds, and also to make the construction of the apparatus extremely simple and compact so that the waste of installation space can be eliminated, and the manufacturing cost can be greatly reduced.

[Solution] [The apparatus of the present invention] is equipped with a chemical solution injection needle (50A) whose movement is controlled (in a manner that allows positioning) between an alternate rack mounting part (7) and a reaction block (6) equipped with an agitating means which forms a rotating magnetic field that causes a magnet (5c) sunk into each reaction tube (5) to rotate, and a temperature control means (12) which heats or cools each reaction tube (5); furthermore, the apparatus is arranged so that a reagent rack (33) in which test tubes (32) each containing a specified amount of a reagent are disposed, a sample rack (35) in which test tubes (34) each containing a specified amount of a compound whose reaction has been completed are disposed, a filtration rack (37) in which filter-equipped filtration cartridges (36) into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, and a column purification rack (39) in which extraction tubes (38) that the compounds whose reactions have been completed to column purification are disposed, can be alternately mounted on the aforementioned alternate rack mounting part (7).



[Claims]

[Claim 1] An automatic compound synthesizing apparatus which is characterized by the fact that in an automatic compound synthesizing apparatus in which reagents stored in respective test tubes (32) disposed in a reagent rack (33) are sucked in and injected in specified amounts into respective reaction tubes (5) disposed in a reaction block (6) by a chemical solution injection needle (50A, 50B) whose movement is controlled so that this chemical solution injection needle can be positioned in the positions of the aforementioned test tubes (32) and the positions of the aforementioned reaction tubes (5), the aforementioned reaction block (6) is equipped with an agitating means (11) which forms a magnetic field that rotates in the circumferential direction of each reaction tube (5) and thus causes a magnetic agitator (5c) sunk into each reaction tube (5) to rotate, and a temperature control means (12) which heats or cools each reaction tube (5), the aforementioned reagent rack (33) is detachably mounted on an alternate rack mounting part (7), and

the aforementioned alternate rack mounting part (7) is formed so that a sample rack (35) in which test tubes (34) each containing a specified amount of a compound whose reaction has been completed, a filtration rack (37) in which filter-equipped filtration cartridges (36) into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, or a column purification rack (39) in which extraction tubes (38) that subject the compounds whose reactions have been completed to column purification are disposed, can be mounted instead of the aforementioned reagent rack (33).

[Claim 2] The automatic compound synthesizing apparatus claimed in Claim 1, in which the temperature control means (12) of the aforementioned reaction block (6) consists of a heater (16) that heats each reaction tube (5), and a circulation passage (17) that causes the external circulation of a coolant that cools each reaction tube (5).

[Claim 3] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] in the aforementioned alternate rack mounting part (7), a drain tank (31) is formed on one side (left or right) of a rack carrying surface (30) that carries the rack.

[Claim 4] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] [i] in the aforementioned alternate rack mounting part (7), a drain tank (31) is formed on one side (left or right) of a rack carrying surface (30) that carries the rack, [ii] in the aforementioned column purification rack (39), a fraction rack (44) in which test tubes (43) that recover the eluate from the aforementioned extraction tubes (38) are disposed is carried on the portion of the aforementioned rack carrying surface (30) where there is no drain tank (31), and a shift rack (45) in which in the extraction tubes (38) that subject the samples whose reactions have been completed to column purification are disposed is installed so that this shift rack (45) can slide in the horizontal direction above the aforementioned fraction rack (44), and [iii] this shift rack (45) is formed so that it is positioned above the aforementioned fraction rack (44) when caused to slide to one end, and so that it is positioned above the drain tank (31) when caused to slide to the other end.

[Claim 5] The automatic compound synthesizing apparatus claimed in Claim 1, [which is characterized by the fact that] the aforementioned alternate rack mounting part (7) is formed so that a TLC substrate supporting rack (61) which supports (in a substantially horizontal attitude) a TLC substrate (60) on which a fixed layer [Translator's note: possibly "fixing layer"] for thin-layer chromatography is formed can be mounted instead of the aforementioned reagent rack (33).

[Claim 6] A sealing structure which is characterized by the fact that aluminum caps (5b) in which through-holes (56) through which a chemical solution injection needle (50A, 50B) is passed are formed are screw-engaged with the upper-end opening parts (59) of reaction tubes (5) in which compounds with arbitrary mixture rates are synthesized by the injection of specified amounts of a plurality of reagents by the aforementioned [reagent injection] needle, elastic packing (5a) is interposed between these aluminum caps (5b) and the upper-end opening parts (59) of the reaction tubes (5), this elastic packing (5a) is formed from silicone rubber (57), and a lining (58) consisting of a fluororesin film is applied to the bottom surface of the packing (5a).

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention] The present invention relates to an automatic compound synthesizing apparatus which synthesizes compounds with arbitrary mixture rates in respective reaction tubes disposed in a reaction block, and a reaction tube sealing structure used in this automatic compound synthesizing apparatus.

[0002]

[Prior Art] Recently, a procedure known as combinatorial chemistry has been used in cases where novel compounds are created by combining several substances. In this procedure, a plurality of different types of reagents prepared beforehand are mixed at arbitrary mixture rates in respective test tubes, so that numerous samples with different mixture rates are synthesized, and compounds with optimal mixture rates are selected from these compounds. In concrete terms, various types of operations are necessary: namely, a reagent injection operation is first performed in which reagents are injected at arbitrary mixture rates into each of a large number of reaction tubs disposed in a rack. Then, a reaction operation is performed in which specified chemical reactions are caused to proceed by agitating the reagents that have been injected into the reaction tubes, and controlling the temperature. Then, in cases where the compounds synthesized by the completion of the reactions are separated into a plurality of liquid layers, a liquid separation operation is performed in which the compounds are sucked in from specified liquid layer portions, and in cases where it is necessary to filter the compounds whose reactions have been completed, a filtration operation is performed; furthermore, a column purification operation is performed in order to analyze the compounds whose reactions have been completed.

[0003] In such cases, extremely large numbers of samples are synthesized, and the abovementioned treatments must be performed for each of these samples. Recently, therefore, a procedure has been adopted in which these various treatments are performed automatically using a reagent injection apparatus, reaction apparatus, liquid separation

apparatus, filtration apparatus and column purification apparatus, etc. In such a procedure, reagents are first injected into the respective reaction tubes at specified mixture rates by the reagent injection apparatus. Next, in the reaction apparatus, since various conditions such as the temperature conditions, time conditions and agitation conditions, etc., under which the chemical reactions are performed are pre-programmed, reactions will proceed according to this program if the respective reaction tubes into which the reagents have been injected at specified mixture rates are set in the reaction apparatus. Then, in cases where the compounds whose reactions have been completed are separated into a plurality of liquid layers, the desired compounds can be extracted from specified portions of the liquid layers by treating these liquid layers with the liquid separation apparatus. If necessary, furthermore, the compounds inside the reaction tubes can be subject to an analysis pre-treatment by the column purification apparatus after being filtered by the filtration apparatus.

[0004]

[Problems to Be Solved by the Invention] However, in cases where such an automated apparatus is used, although the respective operations are automated, only one operation can be performed in each apparatus, so that an automated apparatus must be installed for each operation, thus leading to problems of increased cost and wasteful installation space. Furthermore, in cases where it is attempted to perform these respective operations using a single apparatus, the manufacturing cost is not greatly alleviated merely be concentrating the respective apparatuses [into a single unit], and the resulting apparatus is increased in size so that there is no saving in terms of installation space.

[0005] Accordingly, the technical object of the present invention is to make it possible to perform the various operations required for the synthesis of compounds automatically, and also to make the apparatus extremely compact, so that there is no waste of installation space, and so that the manufacturing cost can be greatly reduced.

[0006]

[Means Used to Solve the Abovementioned Problems] In order to solve the abovementioned problems, the present invention is characterized by the fact that in an automatic compound synthesizing apparatus in which reagents stored in respective reaction tubes disposed in a reagent rack are sucked in and injected in specified amounts into respective reaction tubes disposed in a reaction block by a chemical solution injection needle whose movement is controlled so that this chemical solution injection needle can be positioned in the positions of the aforementioned test tubes and the positions of the aforementioned reaction tubes, the aforementioned reaction block is equipped with an agitating means which forms a magnetic field that rotates in the circumferential direction of each reaction tube and thus causes a magnetic agitator sunk into each reaction tube to rotate, and a temperature control means which heats or cools each reaction tube, the aforementioned reagent rack is detachably mounted on an alternate rack mounting part, and the aforementioned alternate rack mounting part is formed so that a sample rack in which test tubes each containing a specified amount of a compound whose reaction has been completed, a filtration rack in which filter-equipped filtration cartridges into each of which a specified amount of a compound whose reaction has been completed is injected and filtered are disposed, or a column purification rack in

which extraction tubes that subject the compounds whose reactions have been completed to column purification are disposed, can be mounted instead of the aforementioned reagent rack.

[0007] In the present invention, a reagent rack, a sample rack, a filtration rack and a column purification rack can be alternately mounted on the alternate rack mounting part. Accordingly, if the reagent rack is mounted in cases where a reagent injection operation is to be performed, the reagents contained in the respective test tubes of the reagent rack can be sucked in by the chemical solution injection needle and injected into the respective reaction tubes disposed in the reaction block. Next, since the reaction block is equipped with an agitating means which forms a rotating magnetic field that rotates magnets sunk into each reaction tube, and a temperature control means that heats or cools each reaction tube, a reaction operation can be performed which causes specified chemical reactions to proceed while agitating the reagents injected into the reaction tubes and controlling the temperature in this location.

[0008] Furthermore, in cases where a liquid separation operation is to be performed, it is sufficient to mount the sample rack on the alternate rack mounting part, to suck in the compounds from specified liquid phases in the reaction tubes by means of the chemical solution injection needle, and to discharge these compounds into the test tubes of the sample rack. Moreover, in cases where a filtration operation is to be performed, it is sufficient to mount the filtration rack on the alternate rack mounting part, and to discharge the compounds sucked in by the chemical solution injection needle from the reaction tubes disposed in the reaction block or the test tubes disposed in the sample rack carried on the reaction block into the filtration cartridges of the filtration rack. Furthermore, in cases where a column purification reaction is to be performed, it is sufficient to mount the column purification rack on the alternate rack mounting part, and to discharge the compounds sucked in by the chemical solution injection needle into the extraction tubes of the column purification rack. Thus, various operations can be performed automatically in a single apparatus, merely by exchanging the racks mounted on the alternate rack mounting part. Accordingly, the apparatus itself can be made extremely compact, and the manufacturing cost is also reduced.

[0009]

[Working Configurations of the Invention] A working configuration of the present invention will be concretely described below with reference to the attached figures. Figure 1 is a front view which shows the automatic compound synthesizing apparatus of the present invention. Figure 2 is a sectional view along line I-I in Figure 1. Figure 3 is an enlarged view which shows the internal structure of the reaction block. Figure 4 is a front view which shows the sample rack mounted on the alternate rack mounting part. Figure 5 is a front view which shows the TLC substrate supporting rack mounted on the alternate rack mounting part. Figure 6 is a front view which shows the filtration rack mounted on the alternate rack mounting part. Figure 7 is a front view which shows the column purification rack mounted on the alternate rack mounting part. Figure 8 is a fluid circuit diagram which shows the piping system. Figure 9 is an enlarged view which shows [one of] the reaction tubes and the sampling needle. Figure 10 is an enlarged view which shows [one of] the extraction tubes and the column purification needle.

[0010] In the automatic compound synthesizing apparatus of the present embodiment, a transparent door 3 is attached to the front of a box-form main body 2. When this door 3 is opened, a reaction block 6 in which reaction tubes 5, 5 with a volume of 5 cc are disposed is installed (for example) on the left front part of the base 4 of the main body 2, and an alternate rack mounting part 7 on which various types of racks can be detachably mounted is formed on the right front part [of the base 4]. Furthermore, a robot arm 9 whose movement is controlled in the directions of three orthogonal axes is disposed on the overhead part 8 of the main body, and can be positioned in the positions of the reaction tubes 5 disposed in the reaction block 6 or the positions of the test tubes disposed in the racks mounted on the alternate rack mounting part 7.

[0011] In the reaction tubes 5, caps 5b which have elastic packing 5a formed in a two-layer structure consisting of silicone rubber and a fluororesin film are mounted on the upper-end opening parts 59, and magnetic agitators 5c which have N and S poles formed on both ends are suck into the interiors of the reaction tubes 5. More concretely, an aluminum cap 5b in which a through-hole 56 through which the chemical solution injection needle 50A or 50B (described later) is passed is screw-engaged with the upper-end opening part 59 of [each] reaction tube 5, and elastic packing 5a is interposed between this aluminum cap 5b and the upper-end opening part 59 of the reaction tube 5. This elastic packing 5a is formed from a dimethylsilicone rubber which has a hardness HsA of approximately 20 to 25 as measured by a JIS-A type hardness testing machine, and a lining 58 consisting of a fluororesin film with a thickness of approximately 100 μm is applied to the bottom surface of the packing. For example, a tetrafluoroethylene-hexafluoropropylene copolymer film is used as this fluororesin film.

[0012] In the reaction block 6, accommodating holes 10 ... in which reaction tubes 5 with a volume of (for example) 5 cc are accommodated in the form of a matrix at a fixed spacing are opened in the upper surface, and the reaction block 6 is equipped with an agitating means 11 which forms a rotating magnetic field that rotates in the circumferential direction of the respective reaction tubes 5 and causes the rotation of magnetic agitators 5c that are sunk into the reaction tubes 5, and a temperature control means 12 which heats or cools the respective reaction tubes 5, in a state in which these reaction tubes 5 ... are accommodated in the respective accommodating holes 10 .... Furthermore, a cooling manifold 13 which cools the caps 5b of the reaction tubes 5 during heated reactions in a state in which the reaction tubes 5 are mounted is attached to the reaction block 6. Moreover, this reaction block 6 can be removed from the automatic synthesizing apparatus 1 if necessary.

[0013] In the agitation means 11, rotating shafts 14 which have permanent magnets 14a attached to their tip ends are disposed beneath the respective accommodating holes 10, and pulleys 14b are attached to the other ends of these rotating shafts 14. A plastic belt 14c is mounted on these pulleys 14b so that [the rotating shafts 14] can be rotationally driven by a motor 15. Furthermore, the temperature control means 12 consists of an electric heater 16 which heats the reaction tubes 5 accommodated in the accommodating holes 10, and a circulation passage 17 which allows the external circulation of a coolant that cools the respective reaction tubes 5. The heater 16 is powered, or a coolant is caused to flow through the circulation passage 17, in accordance with a set temperature.

[0014] Furthermore, the cooling manifold 13 is attached to the reaction block 6 via a hinge 18, so that the cooling manifold 13 can be opened and closed, and a cooling block 20 in which recesses 19 that cover the caps 5b of the respective reaction tubes 5 are formed is disposed on the bottom surface side of the manifold 13, and a circulation passage 21 which allows the external circulation of a coolant is formed in this cooling block 20. Furthermore, each of the aforementioned recesses 19 is opened on the upper surface side via a through-hole 22 into which the sampling needle (chemical solution injection needle, described later) is inserted. These through-holes 22 are closed off by two silicone rubber sheets 23A and 23B that are disposed with a specified spacing, and the spaces between the silicone rubber sheets in the respective through-holes 22 are connected via a nitrogen gas supply passage 24.

[0015] In the alternate rack mounting part 7, a rack carrying surface 30 which carries the various types of racks is formed, and a drain tank 31 is formed on one side (left or right) of this carrying surface 30. Furthermore, a reagent rack 33 in which a plurality of test tubes 32 that contain reagents are disposed, a sample rack 35 in which test tubes 34 that each contain a specified amount of a compound whose reaction has been completed are disposed, a filtration rack 37 in which filter-equipped filtration cartridges 36 into which specified amounts of compounds whose reactions have been completed are injected and filtered, a column purification rack 39 in which extraction tubes 38 that subject compounds whose reactions have been completed to column purification are disposed, and a TLC substrate supporting rack 61 which supports (in a substantially horizontal attitude) TLC substrates 60 that are used in thin-layer chromatography for the analysis of compounds during the reactions or compounds whose reactions have been completed, are formed so that these racks can be mounted on the rack carrying surface 30.

[0016] In the filtration rack 37, a cartridge rack 42 in which filtration cartridges 36 are disposed at the same pitch as test tubes 40 is detachably mounted on the upper surface of a rack main body 41 in which the abovementioned test tubes 40 are disposed, and the filtration cartridges 36 are formed so that only the filter parts 36a of these cartridges can be replaced.

[0017] In the column purification rack 39, a fraction rack 44 in which test tubes 43 are disposed is carried on the portion of the rack carrying surface 30 where there is no drain tank 31, and a shift rack 45 in which extraction tubes 38 that subject the compounds whose reactions have been completed to column purification are disposed is installed so that this shift rack 45 can slide in the horizontal direction above the aforementioned fraction rack 44. This shift rack 45 is formed so that it is positioned directly above the aforementioned fraction rack 44 when caused to slide to one end, and so that it is positioned directly above the drain tank 31 when caused to slide to the other end.

[0018] The TLC substrates 60 that are supported on the TLC substrate rack 61 are formed by (for example) kneading a powdered adsorbing agent such as silica gel, alumina or cellulose, etc., together with calcined gypsum, etc., and fixing this mixture to a glass substrate or aluminum substrate, thus forming a thin layer that acts as a fixed layer for thin-layer chromatography. Furthermore, the TLC substrates 60 may consist of a single large substrate that can be carried on the substrate supporting rack 61, or relatively small substrates formed by splitting such a large substrate into a plurality of substrates.

Furthermore, a single large substrate may be formed so that this substrate can be split if necessary.

[0019] Furthermore, a sampling needle (chemical solution injection needle) 50A which injects reagents into the reaction tubes 5 and sucks in reagents from the reaction tubes 5, and a column purification needle (chemical solution injection needle) 50B which injects compounds or solvents into the reaction tubes 38 when column purification is performed, can be alternately attached to the robot arm 9. This sampling needle 50A is formed with a pointed tip so that it can pierce the elastic packing 5a mounted in the cap 5b of each reaction tube 5; furthermore, a flow passage 50a which sucks in and injects reagents is opened in the tip end of the needle, and a discharge flow passage 50b which discharges the air inside the reaction tube 5 to the outside when the needle 50A has pierced [the packing] is opened in the lower end and upper end of the needle 50A. Furthermore, in cases where acidic reagents such as hydrochloric acid or sulfuric acid, etc., are injected as reagents, a sampling needle 50A is used in which at least the portions [of the needle] that form the flow passage 50a are formed by an acid-resistant metal such as Hastealloy C, etc. Furthermore, the tip end of the column purification needle 50B is formed with a spherical surface shape, so that this tip end adheres tightly to the recess 38c of the cap 38b that is inserted into the upper end of the corresponding extraction tube 38 filled with a filling agent 38a.

[0020] Furthermore, the robot arm 9 is equipped with a piping system 51 that sucks in or discharges reagents, and injects solvents. A port 52 which is connected to the aforementioned needle 50A or 50B is formed in one end of this piping system 51, and a plurality of solvent bottles M_1 through M_n are connected in a switchable manner to the other end of the piping system 51 via a switching valve CV. A digitally controlled syringe pump 53 is interposed as a flow rate controlling pump that can switch the direction of intake and discharge. Accordingly, using this sampling needle 50A, specified amounts of reagents can be sucked in from the test tubes 32 disposed in the reagent rack 33, and these reagents can be discharged in specified amounts into each of the reaction tubes 5 disposed in the reaction block 6. Furthermore, solvents from the solvent bottles M_1 through M_n can be discharged in specified amounts into each of the reaction tubes 5, and the compounds whose reactions have been completed in the reaction tubes 5 can be sucked in and discharged into the test tubes 34 disposed in the sample rack 35 or the filtration cartridges 36 disposed in the filtration rack 37. Furthermore, using the column purification needle 50B, specified amounts of specified solvents can be discharged into the extraction tubes 38 disposed in the column purification rack 39 from the solvent bottles M_1 through M_n, and compounds whose reactions have been completed can be sucked in and discharged in specified amounts.

[0021] Furthermore, 54A and 54B are needle holders that accommodate the aforementioned needles 50A and 50B. Cleaning devices (not shown in the figures) that blow a cleaning liquid or pressurized air onto the tip ends of the needles 50A and 50B are installed inside these holders. Furthermore, 55 indicates a multi-unit pressurizing nozzle that fills the interiors of the filtration cartridges 36 with nitrogen gas under pressure when filtration is performed.

[0022] The above is an example of the construction of the present invention; next, the operation of the present invention will be described. When compounds are synthesized,

for example, (1) a reagent injection operation, (2) a solvent injection operation, (3) a reaction operation, (4) a TLC analysis operation, (5) a liquid separation sampling operation, (6) a filtration operation, and (7) a column purification operation, are performed. Accordingly, these operations will be described.

[0023] The reagent injection operation is an operation in which reagents contained in the respective test tubes 32 disposed in the reagent rack 33 are sucked in an injected in specified amounts into each of the aforementioned reaction tubes 5 disposed in the reaction block 6 in order to synthesize compounds with arbitrary mixture rates in these reaction tubes 5. In this case, the reaction tubes 5 are first mounted in the accommodating holes 10 of the reaction block 6, after which the upper surface [of the reaction block 6] is covered by the cooling manifold 13. Meanwhile, the reagent rack 33 in which a plurality of test tubes 32 containing reagents are disposed is mounted on the alternate rack mounting part 7. In this state, when the reagent injection amounts are set for each reaction tube 5, the sampling needle 50A is mounted on the tip end of the robot arm 9, and the movement of this sampling needle is controlled so that the reagent in [one of] the aforementioned test tubes 32 is sucked in and discharged in specified amounts into each of the reaction tubes 5. Afterward, the sampling needle 50A is cleaned by the cleaning device inside the needle holder 54A. Next, the reagent in a different test tube 32 is discharged into each of the reaction tubes 5. This process is repeated so that reagents of the required types are injected into each of the reaction tubes 5 at an arbitrary mixture rate.

[0024] Next, a solvent injection operation is performed if necessary. This is an operation in which a specified amount of a solvent is discharged into each of the reaction tubes 5 in cases where it is necessary to use a solvent in the synthesis of the compound in question. In this case, required solvents from the respective solvent bottles M_1 through M_n are injected into each of the reaction tubes 5 using the sampling needle 50A. Here, furthermore, in cases where an acidic solvent such as hydrochloric acid or sulfuric acid, etc., is injected, an acid-resistant needle in which at least the internal flow passage 50a is formed from an acid-resistant metal is used as the sampling needle 50A.

[0025] After a plurality of reagents have thus been injected at arbitrary mixture rates into each of the reaction tubes 5, a reaction operation is performed. This is an operation in which a reaction is caused to proceed under preset conditions with specified temperature and time control by controlling the agitation and temperature. In cases where agitation is performed, starting the motor 15 of the agitation means 11 causes the permanent magnets 14a to rotate, so that a rotating magnetic field is formed in each accommodating hole 10, thus causing the magnetic agitator 5c that is sunk into each reaction tube 5 to rotate, so that the chemical solution in each reaction tube 5 is agitated. Furthermore, in cases where temperature control is performed, the heater 16 is powered if the set temperature is greater than room temperature, and a coolant supplied from the outside is circulated through the circulation passage 17 if the set temperature is lower than room temperature, so that a reaction is caused to proceed under specified temperature conditions.

[0026] Furthermore, in cases where the reaction tubes 5 are heated, there is a danger that the reaction solvent in the reaction tubes 5 will leak to the outside so that the concentration of the reaction solution changes. Accordingly, in this case, the spaces around the reaction tubes 5 are filled with nitrogen gas from the nitrogen gas supply

passage 24 formed in the cooling manifold 13, so that the reaction tubes 5 are placed in a nitrogen gas atmosphere. In this sate, a coolant is supplied to the circulation passage 21 so that the caps 5b of the reaction tubes 5 are cooled. In particular, if aluminum, which is superior in terms of thermal conductivity, is used as the material of the caps 5b, then the elastic packing 5a inside each reaction tube 5 and the vicinity of the upper-surface opening part 59 can be cooled by cooling the caps 5b. As a result, the reaction solvent that is evaporated inside the reactions tubes 5 is cooled by the caps 5b so that this reaction solvent condenses and is returned to the interiors of the reaction tubes 5. Accordingly, there is no change in the concentration of the reaction solution inside the reaction tubes 5. Furthermore, since the reaction tubes 5 are placed in a nitrogen gas atmosphere, there is no condensation around the reaction tubes 5, especially on the caps 5b, and even if some condensation should occur, the upper-surface opening parts 59 are closed off in an air-tight state by the elastic packing 5a, so that water droplets do not enter the interiors of the reaction tubes 5. Moreover, when an experiment was performed in which the elastic packing 5a of the present example in which a lining 58 consisting of a fluororesin film was formed on the bottom surface of a silicone rubber [part] 57, and 100% methanol was placed in the reaction tubes 5 and heated for 24 hours while the caps 5b were cooled, the amount of decrease in the contents of the reaction tubes was approximately 0.18% on the average, thus confirming that extremely good sealing characteristics can be obtained.

[0027] Next, at the point in time where the reaction is completed, a reaction stopping agent (e. g., water) is injected so that the progress of the reaction is halted. Then, if necessary, a TLC analysis operation using thin-layer chromatography is performed in order to check whether or not the desired compound has been purified, and in some cases, such an operation is performed before the reaction is completed in order to check the composition during the reaction. This TLC analysis operation is especially useful for checking which liquid layer contains the purified target compound in cases where the synthesized compound is separated into a plurality of liquid layers. In concrete terms, the reagent rack 33 is removed, the TLC substrate supporting rack 61 is mounted, and specified amounts of the compound are dropped onto the TLC substrates 60 supported on this rack 61 from the respective liquid layers, and are then developed on the TLC substrates 60, after which an analysis is performed by irradiation with ultraviolet radiation, etc.

[0028] Then, the desired compound synthesized in each reaction tube 5 is removed. In this case, the reagent rack 33 or TLC substrate supporting rack 61 mounted on the alternate rack mounting part 7 is first removed, and the sample rack 35 is mounted. Here, in cases where the compounds synthesized in the reaction tubes 5 are colloidal, and are not separated into liquid layers, there is no need to determine the positions of liquid layers; accordingly, it is sufficient in such cases merely to suck in the compounds in the reaction tubes 5 by means of the sampling needled 50A. On the other hand, in cases where the synthesized compounds are separated into a plurality of liquid layers, liquid layer sampling is performed, and the chemical solution in the liquid layer portion in which the target compound is purified is collected. This is accomplished by setting the position of the liquid layer inside the reaction tube 5, positioning the tip end of the sampling needle 50A inside this liquid layer and sucking in the compound, and

discharging the sucked-in compound into one of the test tubes 34 in the sample rack 35. This operation is performed for each reaction tube 5.

[0029] Furthermore, in cases where it is necessary to filter the compounds whose reactions have been completed, the filtration rack 37 is mounted so that it is positioned directly above the drain tank 31 of the alternate rack mounting part 7. Then, in cases where the compounds collected in the test tubes 34 of the sample rack 35 are to be filtered, the sample rack 35 is mounted on the reaction block 6, and the compounds in the test tubes 34 are sucked in and injected into the filtration cartridges 36 by means of the sample needle 50A. On the other hand, in cases where the compounds are injected directly into the filtration cartridges 36 from the reaction tubes 5, the compounds in the reaction tubes 5 are sucked in and injected into the filtration cartridges 36 by means of the sample needle 50A. Next, if necessary, the filtration time can be shortened by using the multi-unit pressurizing nozzle 55 to supply pressurized nitrogen gas to the filtration cartridges 36.

[0030] Furthermore, in cases where a column purification operation is to be performed as a pre-treatment for the structural analysis of the synthesized compounds, the column purification rack 39 is mounted on the alternate rack mounting part 7. In this case, test tubes 43 are first accommodated in the fraction rack 44, extraction tubes 38 are accommodated in the shift rack 45, and this shift rack 45 is caused to slide to the side of the drain tank 31. In this state, the column purification needle 50B is mounted on the tip end of the robot arm 9, and conditioning is performed by injecting a specified solvent into the respective extraction tubes 38.

[0031] Next, when conditioning is completed, sample loading is performed in which the samples sucked in from the sample rack 35 mounted on the reaction block 6 are injected into the respective extraction tubes 38. In this case, each time that one sample is injected into one extraction tube 38, the tip end of the column purification needle 50B is cleaned by the cleaning device inside the needle holder 54B so that the mixing of samples is prevented.

[0032] When sample loading is completed, a cleaning operation which washes away foreign matter held in the fixed layers of the extraction tubes 38 is performed. This is accomplished by injecting a cleaning solvent by means of the column purification needle 50B; in this case, the liquid that flows out of the extraction tubes 38 is recovered in the drain tank 31.

[0033] When the cleaning operation is completed, the shift rack 45 is caused to move to the side of the fraction rack 44, and a specified solvent is injected into the extraction tubes 38 so that the eluates are recovered in the respective test tubes 43 of the fraction rack 44, thus completing the column purification operation. In this case, furthermore, instead of recovering the eluates from the extraction tubes 38 directly in the respective test tubes 43, it would also be possible to monitor the eluates by means of an ultraviolet absorption meter so that the concentrations of the eluates or substances contained in the eluates are detected, and to move the fraction rack 44 and automatically change the test tubes 43 to new test tubes 43 each time there is a change in the detected substance or concentration, so that an automatic fractionation is performed with only the ultraviolet absorption peaks taken as fractions. Furthermore, the eluates recovered in the respective

test tubes 43 of the fraction rack 44 can be concentrated in a centrifugal separator, and after these concentrates are dissolved, a structural analysis can be performed using a structural analysis device.

[0034]

[Merits of the Invention] In the present invention, as was described above, respective operations required for the parallel synthesis of compounds, such as a reagent injection operation, a synthesizing reaction operation, a liquid separation sampling operation, a filtration operation and a column purification operation, etc., can be automatically performed using a single apparatus merely by replacing racks mounted on an alternate rack mounting part, so that the following superior merits are obtained: namely, the apparatus itself can be made extremely compact, and the manufacturing cost can be reduced.

[Brief Description of the Drawings]

[Figure 1] Figure 1 is a front view which shows the automatic compound synthesizing apparatus of the present invention.

[Figure 2] Figure 2 is a sectional view along line I-I in Figure 1.

[Figure 3] Figure 3 is an enlarged view which shows the internal structure of the reaction block.

[Figure 4] Figure 4 is a front view which shows the sample rack mounted on the alternate rack mounting part.

[Figure 5] Figure 5 is a front view which shows the TLC substrate supporting rack mounted on the alternate rack mounting part.

[Figure 6] Figure 6 is a front view which shows the filtration rack mounted on the alternate rack mounting part.

[Figure 7] Figure 7 is a front view which shows the column purification rack mounted on the alternate rack mounting part.

[Figure 8] Figure 8 is a fluid circuit diagram which shows the piping system.

[Figure 9] Figure 9 is an enlarged view which shows [one of] the reaction tubes and the sampling needle.

[Figure 10] Figure 10 is an enlarged view which shows [one of] the extraction tubes and the column purification needle.

[Explanation of Symbols]

1 Automatic compound synthesizing apparatus

5 Reaction tubes

5a Elastic packing

5b Cap

5c Magnetic agitator

6 Reaction block

7 Alternate rack mounting part

11 Agitating means

12 Temperature control means

16 Heater

17 Circulation passage

30 Rack carrying surface

31 Drain tank

32 Test tubes

33 Reagent rack

34 Test tubes

35 Sample rack

36 Filtration cartridges

37 Filtration rack

38 Extraction tubes

39 Column purification rack

43 Test tubes

44 Fraction rack

45 Shift rack

50A Sampling needle (chemical solution injection needle)

50B Column purification needle (chemical solution injection needle)

56 Through-hole

57 Silicone rubber

58 Lining

59 Upper-end opening part

60 TLC substrates

61 TLC substrate supporting rack

Figure 1

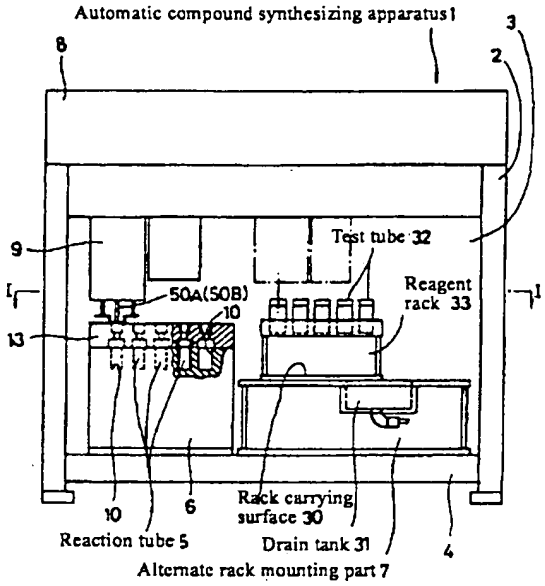


Figure 2

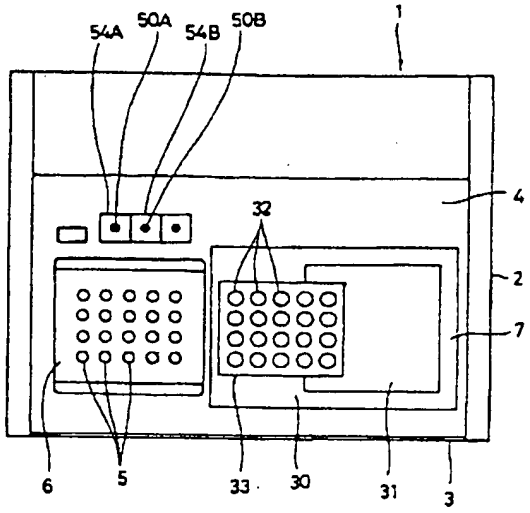


Figure 4

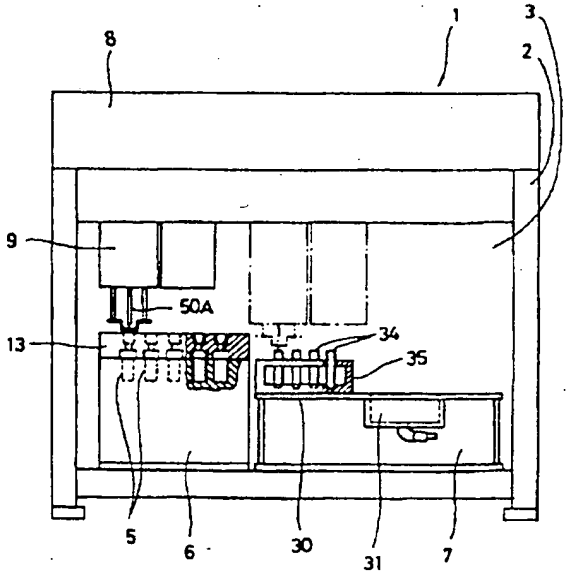


Figure 7

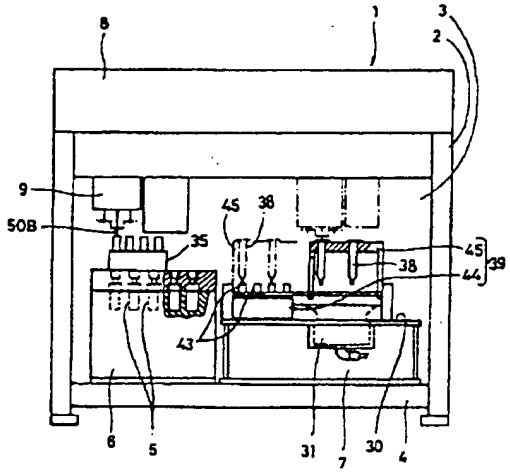


Figure 3

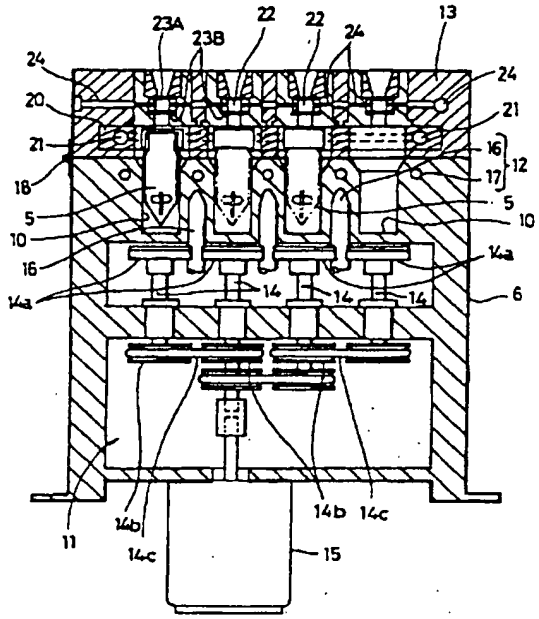


Figure 5

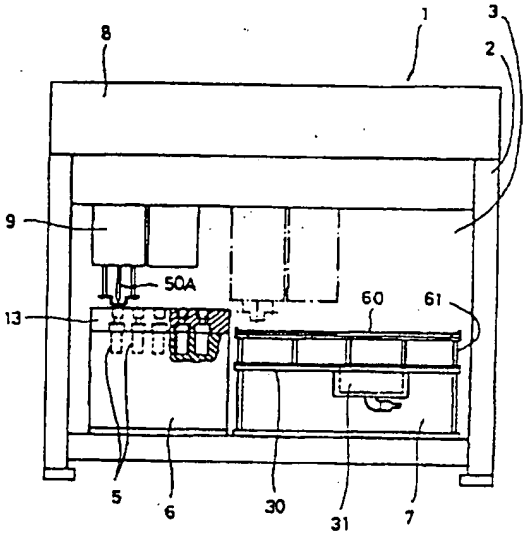


Figure 9

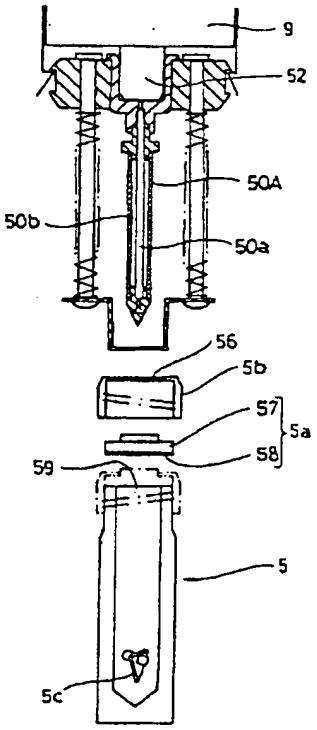


Figure 6

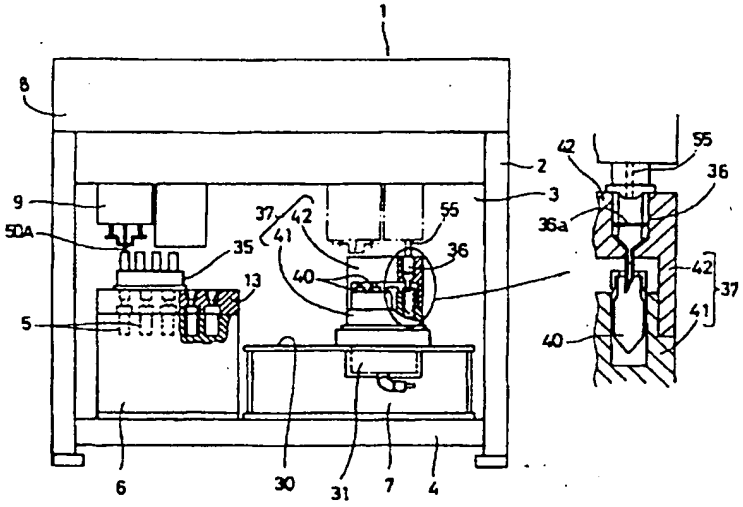


Figure 8

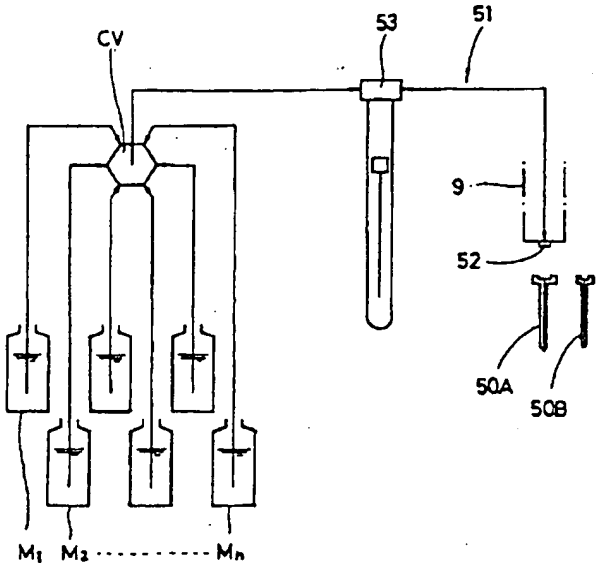
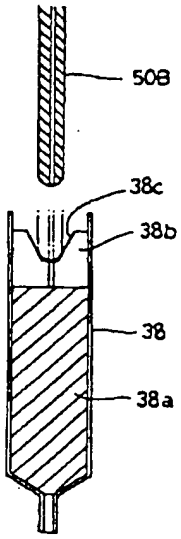


Figure 10



L21 ***ANSWER 113 OF 173*** CA COPYRIGHT 2001 ACS
AN 116:215207 CA
TI Batch multistage polymerization apparatus
IN Nakazato, Norio; Oda, Chikao; Nakamoto, Hidekazu; Ihara, Kazuo
PA Hitachi, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp. CODEN: JKXXAF
PI JP 04018424 A2 19920122 JP 1990-36061 19900219
AB An app. for manuf. of polymers with high quality and high yield consists of multiple reactors, and a reaction monitor control app. which evaluates the polymn. state, e.g., viscosity, and det. the polymn. conditions for the following stages. A diagram of this app. is included.

COMPOUND AUTOMATICALLY SYNTHESIZING APPARATUS AND SEALING STRUCTURE FOR REACTION TUBE USED THEREFOR

Patent number: JP10182501
Publication date: 1998-07-07
Inventor: KOIKE TOSHIO
Applicant: MORITEX CORP
Classification:
- international: C07B61/00; C09K3/10
- european:
Application number: JP19970238644 19970903
Priority number(s):

Abstract of **JP10182501**

PROBLEM TO BE SOLVED: To provide the subject apparatus capable of automatically carrying out various operations required for synthesis of compound, being constituted extremely compactly and simply, omitting the uselessness of installation space and greatly reducing a production cost.

SOLUTION: This apparatus comprises a reagent rack 33 which is equipped with a chemical injecting needle 50A to be moved and controlled between a reaction block 6 provided with a stirring means for forming a rotary magnetic field by rotating a magnet sunk in each reaction tube 5 and with a temperature control means for heating or cooling each reaction tube 5 and an exchange rock fitting part 7 so as to freely determine a position and is furnished with arranged test tubes 33 for preserving each fixed amount of the reagent on the exchange rack fitting part 7, a sample rack provided with arranged test tubes for storing each fixed amount of a compound having finished a reaction, a filtration rack provided with arranged cartridges with a filter for injecting a fixed amount of the compound having finished reaction and filtering or a column purifying rack provided with extraction tubes for purifying the compound having finished reaction by columns. These racks are exchanged and fixed.